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Treatment of out-of-hospital status epilepticus with diazepam rectal gel

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Intravenous access cannot always be promptly obtained when treating status epilepticus outside the hospital. We compared the efficacy and safety of diazepam rectal gel to IV lorazepam in our long-term care facility for adults with developmental disabilities. Diazepam rectal gel was given more quickly and reliably, reducing total seizure time, potential neuronal injury and other complications. A treatment protocol for treating status epilepticus with diazepam rectal gel is given.

Key words: diazepam; status epilepticus; rectal.

INTRODUCTION

Convulsive status epilepticus, especially the generalised type, is an emergency with risk of substantial morbidity and mortality. Its treatment should focus on an operational definition with the primary goal of prompt cessation of seizures. Early treatment reduces total seizure time and improves medication response, and may decrease potential neuronal injury and other complications[1,2]. Many emergency rooms and hospitals have standard protocols, usually involving IV lorazepam.

When status epilepticus occurs outside the hospital or when IV access is not possible, alternative routes for drug administration must be used[3]. At Fircrest it has been very difficult to reliably and quickly obtain IV access in our residents because of muscular contractures and atrophy, seizure movements and obesity. A protocol is followed at Fircrest to eliminate treatment delay and to avoid excessive use of emergency paramedic ambulance service.

Rectal diazepam is an effective and safe treatment for prolonged seizures outside the hospital[4,5]. It achieves blood levels adequate for seizure treatment more rapidly than any route except for the IV one[6]. Diazepam is absorbed more quickly by the rectal route than lorazepam because it is more lipid soluble. Rectal diazepam solution was not used widely at Fircrest because it tended to leak out of the rectum, leading to inaccurate dosing and treatment failure. In 1997, diazepam became available as a rectal gel formulation contained in a pre-filled, rectal syringe (Diastat®) that provides easy and rapid administration. It has rapid, consistent absorption[7]. In placebo-controlled studies, it has been proven safe and effective in treating out-of-hospital acute repetitive seizures[8,9]. It has FDA approval for acute repetitive seizures but not for status epilepticus[10]. Anecdotal reports mention its successful use in status epilepticus. These cases involve rural settings and ER patients with difficult IV access. There is a lack of systematic studies on its efficacy and safety in status epilepticus, especially in adults.

Buccal midazolam[11,12] and intranasal midazolam[13–15] are other potential treatment options. These novel seizure treatments are not as well studied as rectal diazepam and require further investigation to document their efficacy, proper dosing and safety.

METHOD

Fircrest is a state-operated long-term care facility housing 300 severely developmentally disabled adults, many of whom have medically intractable epilepsy. It provides a highly structured environment

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with 24-hour nursing care and staff physicians. Witnessed seizures are routinely documented on our designated seizure sticker form and placed in the patient's chart. The seizure sticker contains the following: date, time of start and end of seizure, seizure characteristics checklist (twitch, jerk, upper body, whole body, bit tongue, blue face, loss of consciousness and wet pants) and signature. Nurses routinely document medication administration time and other patient information in the chart.

Nurses initiated a treatment attempt for status epilepticus after 10 minutes of continuous generalised tonic-clonic seizure activity. From 1st May 1996 to 30th April 1998 this treatment consisted of 4 mg of IV lorazepam; from 1st May 1998 to 1st May 1999, for the same individuals, it consisted of 15–20 mg of diazepam rectal gel. The following data were retrospectively reviewed: time of administration, time to cessation of seizure, time of total seizure and adverse drug reactions. This study was approved by Fircrest's Human Rights Committee.

All individuals with at least one treatment attempt of both diazepam and lorazepam were included in our study population. Paired *t* test was done to statistically analyse how the same patients responded to the two treatments. Of the six patients in our study population, five were female. The average patient age was 29 (range 20–39 years). The average patient body weight was 48 (range 36–64 kg). Five were white and one was Native American in race.

RESULTS

The outcome of 107 total treatment attempts is summarised in Tables 1–3. Data included multiple treatment attempts of both medications for each individual. This shows that diazepam was administered in all 36 attempts whereas lorazepam in 21 out of 71 attempts (30%). The time to administration of diazepam was significantly shorter than lorazepam. There was a significant reduction (27%) of total seizure time

Table 1: Intravenous lorazepam results.

Patient	Time (minute)[a]			Treatments	Dose (mg; mg kg^{-1} dosage)
	To administer	To stop seizure	Total seizure		
1	16 ± 5	5 ± 2	22 ± 3	5	4 (0.11)
2	20 ± 6	4 ± 2	24 ± 6	5	4 (0.06)
3	21 ± 9	4 ± 3	25 ± 12	2	4 (0.09)
4	32 ± 17	5 ± 0	37 ± 17	2	4 (0.1)
5	30 ± 6	6 ± 3	37 ± 10	2	4 (0.09)
6	15 ± 3	3 ± 0	18 ± 3	5	4 (0.06)
Total	20 ± 3	4 ± 1	25 ± 3	21	4 (0.08 ± 0.01)

[a] Time to administer from start of seizure and to stop from administration.

Table 2: Diazepam rectal gel results.

Patient	Time (minute)			Treatments	Dose (mg; mg kg^{-1} dosage)
	To administer	To stop seizure	Total seizure		
1	12 ± 2	6 ± 1	18 ± 2	8	15 (0.42)
2	11 ± 4	7 ± 1	19 ± 4	5	20 (0.33)
3	17 ± 4	8 ± 3	26 ± 6	6	15 (0.33)
4	12 ± 2	3 ± 0.5	15 ± 2	2	15 (0.37)
5	10 ± 1	6 ± 1	16 ± 2	5	15 (0.34)
6	8 ± 1	7 ± 1	16 ± 2	10	20 (0.31)
Total	12 ± 1	7 ± 1	18 ± 1	36	17 (0.35 ± 0.02)

Table 3: Comparison of treatments: rectal diazepam gel and IV lorazepam.

Treatment	Successful administration (%)	Mean time (minute)			Responders within 10 minutes (%)
		To administer	To stop seizure	Total seizure	
Diazepam gel	100	12 ± 1*	7 ± 1**	18 ± 1*	83
IV Lorazepam	30	20 ± 3*	4 ± 1**	25 ± 3*	95

* $P < 0.05$, paired *t* test; ** $P > 0.05$, paired *t* test.

for diazepam compared to lorazepam. After a single dose of either medication, 83% of patients responded within 10 minutes after diazepam whereas 95% after lorazepam. Within 20 minutes all patients responded. In the diazepam treatment attempts, four seizures (11%) were longer than 30 minutes whereas in the lorazepam attempts 20 seizures (28%) exceeded 30 minutes. One episode of transient hypotension resolved without sequelae for both treatments. No respiratory difficulties were reported.

DISCUSSION

A key finding was that diazepam rectal gel was actually administered in all 36 attempts whereas IV lorazepam was administered in only 21 of 71 attempts (30%). This clearly shows how difficult it is to give IV lorazepam in these patients. In addition, even when IV lorazepam was actually given, the average time to administration was 20 minutes whereas diazepam rectal gel was given significantly faster ($P < 0.002$) at an average of 12 minutes into seizure. This is the basis for the superior response to rectal diazepam treatment.

When either medication was actually given, seizures stopped quickly without significant difference ($P < 0.063$), in an average of 4 minutes for lorazepam and 7 minutes for diazepam. Lorazepam worked faster but not enough to compensate for the long treatment delay due to difficulties of IV administration. Also, when medication was actually given, average total seizure time proved to be significantly shorter ($P < 0.026$) after diazepam (18 minutes) than after lorazepam (25 minutes).

Regarding treatment attempts in which medication was not necessarily given, we found that in the diazepam attempts, four seizures (11%) lasted longer than 30 minutes whereas in the lorazepam attempts, 20 seizures (28%) exceeded 30 minutes. This is important because when a patient seizes for more than 30 minutes at our facility, it is likely that we will call the emergency paramedic ambulance service to transfer the patient out to an emergency room.

Two factors may have contributed to the success of diazepam rectal gel. First, it was given reliably and quickly. Second, the average body weight of our patients was low (48 kg), leading to a higher relative dosage (0.3 mg kg^{-1}).

A limitation of our study is the small number of patients. Further study is needed involving a larger number of individuals in a prospective fashion. Since our results indicate the unsuitability of IV treatment for most of our patients, other routes of benzodiazepine administration, such as buccal and intranasal midazolam, require further investigation.

As a result of our findings, we currently implement a diazepam rectal gel protocol for status epilepticus at our facility. This incorporates the current recommendation to initiate treatment after 5 minutes[1]. During a seizure the emergency paramedic ambulance service may be called at any time if the seizure is extremely severe. Respiratory rate and blood pressure are monitored during and after the seizure. Pulse oximeter, oxygen, bag-valve mask ventilator and emergency medications are available if needed. Our protocol is initiated after a generalised tonic-clonic seizure lasting at least 5 minutes or two generalised tonic-clonic seizures within 1 hour between which there is incomplete recovery of consciousness. The *first* step is administration of 20 mg (15 mg for patients <40 kg) and an IV line is attempted. The *second* step is an additional 10 mg if the seizure continues for 10 minutes after the initial dose. If possible give 4 mg of IV lorazepam instead. The physician is notified. The *third* step is to call the emergency paramedic ambulance service if the seizure continues for 10 minutes after the second dose.

CONCLUSIONS

In this patient population, diazepam rectal gel typically can be administered more quickly and reliably than IV lorazepam, reducing seizure duration, potential neuronal injury and other potential complications. It is an appropriate and effective treatment for status epilepticus in this setting.

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